REMARKS

Claims 1-5, 17-22, and 42-71 are active and present in the application.

Request for Reconsideration

The present invention provides particle-based sensors that do not require heating, allowing these sensors to be used not only in laboratories, but by consumers in their homes, or by technicians in the field. The invention is based on the unexpected and surprising results that were obtained by, *inter alia*: (1) altering the alignment of the particles from head-to-tail to tail-to-tail; and (2) using particles having an average diameter of at least 30 nm.

The first discovery was that aggregation of particles in the sensors is influenced by their alignment with respect to each other. In particular, when a "tail-to-tail" alignment is used (as opposed to a tail-to-tail alignment), the particles can aggregate at ambient temperature. Independent claims 1 and 57 specify this "tail-to-tail" arrangement. Since both 3' - and 5' -thiol-modified polynucleotides are needed to produce "tail-to-tail" aligned particles, both types of nucleotides are included in the claims.

The second discovery was that the color of particle aggregates of the sensors is mainly governed by the size of the aggregates. Thus, the rate of aggregation being equal, the rate of color change increases using larger particles, particularly if the particles are at least 30 nm in average diameter. Independent claims 17 and 57 specify that the particles are at least 30 nm in average diameter.

Accordingly, the claims are drawn to sensors that include particles with a "tail-to-tail" arrangement and/or an average diameter of at least 30 nm. Having these features, the sensors do not require heating, allowing for use not only in laboratories, but by consumers in their homes, or by technicians in the field.

The rejection of the claims under 35 U.S.C. § 103(a) as being unpatentable over Cuenoud and Szostak (Nature, vol. 375, pp. 611-614, 1995) in view of Mirkin et al. (U.S. Pat. No. 6,361,944, issued March 26, 2002); Frauendorf and Jaeschke (Bioorganic and Medicinal Chemistry, 9: 2521-2524, 2000) and further in view of Joyce and Breaker (WO 98/49346, 1998) and Li and Lu (J. Am. Chem. Soc., vol. 122, no. 42, pp. 10466-10467, 2000) is respectfully traversed. The claimed invention provides unexpected and surprising

results which demonstrate the unobviousness of the claimed invention. The prior Office Action used an incorrect analysis of this evidence of unobviousness, comparing the invention with a combination of references, rather than the closest prior art.

A greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness of the claims at issue. Applicants must show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage (MPEP, 716.02(a)(I)).

Evidence of unexpected results must compare the claimed invention with the closest prior art. Applicants are not required to compare the claimed invention with subject matter that does not exist in the prior art (MPEP § 716.02(e)(III)). Requiring Applicants to compare the claimed invention with a sensor suggested by the combination of references relied upon in the rejection of the claimed invention "would be requiring comparison of the results of the invention with the results of the invention" (*Id.*).

A comparison of the claimed invention with the disclosure of each cited reference to determine the number of claim limitations in common with each reference, bearing in mind the relative importance of particular limitations, will usually yield the closest single prior art reference (MPEP § 716.02(e)). By this analysis, Li and Lu is the closest single reference.

Independent claim 1 is as follows:

> 1. A sensor system for detecting an effector or cofactor, comprising:
> (a) a nucleic acid enzyme, comprising a cofactor binding site and optionally an effector binding site;
> (b) substrates for the nucleic acid enzyme, comprising first polynucleotides;
> (c) a first set of particles comprising second polynucleotides, wherein the polynucleotides are attached to the particles at the 3' terminus; and
> (d) a second set of particles comprising third polynucleotides, wherein the polynucleotides are attached to the particles at the 5' terminus;
> wherein the first polynucleotides comprise or are at least partially complementary to the second polynucleotides,
> the first polynucleotides comprise or are at least partially complementary to the third polynucleotides, and

> a mixture of (a) the nucleic acid enzyme, (b) the substrates, (c) the first set of particles, and (d) the second set of particles, will form aggregates of the first and second sets of particles, and formation of the aggregates will be at least 95% complete 10 minutes after the mixing.

Independent claim 17 does not include the element that the third polynucleotides are attached to the particles at the 5' terminus the second set of particles; instead, it recites that second set of particles have an average diameter of at least 30 nm. Claim 57 includes both elements.

Li and Lu teaches a sensor including a nucleic acid enzyme having a cofactor binding site (Li and Lu, page 10466, second column, first full paragraph) and a polynucleotide substrate for the nucleic acid enzyme (*Id.*; Fig. 1(a)). Li and Lu, however, does not teach the use of particles. Instead, cleavage of the substrate is detected by means of a fluorescent label and quencher (*Id.*; Fig. 1(b)).

Mirkin et al. is not closer than Li and Lu, since Mirkin et al. fails to disclose a nucleic acid enzyme, a substrate, and the relationship between the first polynucleotide and the second and third polynucleotide. The use of particles is disclosed by Mirkin et al., which teaches the detection of nucleic acids with particles having oligonucleotides attached thereto. Mirkin et al. does state that the "size of nanoparticles is preferably from about 5 nm to about 150 nm (mean diameter), more preferably from about 5 to about 50 nm, most preferably from 10 nm to about 30 nm" (Mirkin et al., col. 17, lines 36-39). However, nowhere does Mirkin et al. teach or suggest the advantage of particles having a diameter of at least 30 nm. Rather, it only uses gold colloids of 13 nm diameter (*Id.*, col. 42, line 58; col. 46, line 46; col. 55, line 51). In Example 15 (*Id.*, cols. 58-59), 3.1 µm latex microspheres are used, but only in conjunction with 13 nm diameter colloidal gold particle probes (*Id.*, col. 58, lines 60-62) which attach to the microspheres in order to detect the presence of the target oligonucleotide (*Id.*, col. 59, lines 6-10). Also, Mirkin et al. is silent as to the advantages of a tail-to-tail arrangement as compared to a head-to-tail arrangement.

Furthermore, Cuenoud and Szostak, Frauendorf and Jaeschke, and Joyce and Breaker are all silent regarding the use of particles.

Applicants may rely on a comparison of the invention that is closer than the closest art cited by the Examiner (MPEP § 716.02(e)(I)). Such a comparison is provided by a sensor including not only a nucleic acid enzyme having a cofactor binding site and a polynucleotide substrate for the nucleic acid enzyme, as taught by Li and Lu, but also 13 nm diameter particles as described by Mirkin et al. This comparison ("Applicants' comparison") features more elements in common with the claims than either of the references, and is therefore closer to the claimed subject matter than the references relied upon in the rejection.

Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims (MPEP § 716.02(b)). Accordingly, the unexpected, superior results of the invention may be demonstrated by a comparison of the invention to Applicants' comparison, which is closer to the invention than the closest reference.

This comparison is illustrated on Figure 4 of the present application, reproduced below.

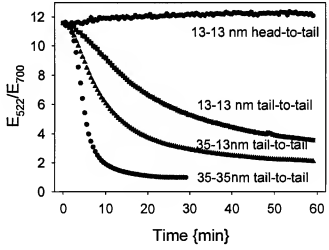


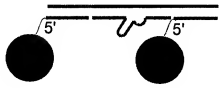
Figure 4

When a mixture of 13 and 35 nm diameter particles is used, the rate of color change is faster than with 13 nm diameter particles alone. The rate of color change further increases if only particles of 35 nm diameter are used. Therefore, the data in the present

application demonstrates the unexpected and superior results obtained over Applicants' comparison. Such results are embodied by independent claims 17 and 57 in their present form.

The comparison on Figure 4 also illustrates the unexpected and superior results that are obtained by aligning the particles in a "tail-to-tail" fashion. Particles may be aligned in two ways, "head-to-tail" or "tail-to-tail" (see Figure 3 of the present application, reproduced below).

A. Head-to-Tail arrangement of gold nanoparticles



B. Tail-to-Tail arrangement of gold nanoparticles

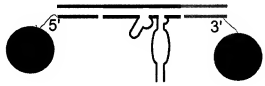


Figure 3

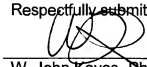
In previous sensors the particles were aligned in the "head-to-tail" fashion (Figure 3A). It appears that in this configuration it is difficult for the particles to aggregate, possibly due to steric effects. Heating and cooling is thus necessary to promote the assembly of particles. However, as illustrated in Figure 4, it has now been discovered that when a "tail-to-tail" (Figure 3B) alignment is used, the rate of color change increases. Such results are embodied by independent claims 1 and 57 in their present form.

As set forth above, the present application provides data demonstrating the unexpected and superior results obtained over Applicants' comparison. As Applicants' comparison is closer to the claimed invention than the closest single reference, the claims

are not obvious over the cited references. Withdrawal of the rejection is respectfully requested.

Applicants submit that the application is in condition for allowance. Early notice of such action is earnestly solicited.

Respectfully submitted,



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